## REMARKS

Claims 1-31 are currently under consideration in the above-referenced patent application and stand rejected under at least one of 35 C.F.R. §§ 112, 102 or 103. Claims 5, 6, 7-14, 17-23, and 25-31 have been canceled from the application; and Claims 1-4, 15, 16, and 24 have been amended as indicated above.

Support for the amendment to Claim 1 is found throughout the application, for example, at page 3, lines 17-31; page 4, lines 4-13; page 6, lines 11-16; page 8, lines 12-19; page 8, line 25, to page 9, line 5; page 9, lines 27-30; page 10, lines 6-10, 23-26 and 30-33; page 14, line 16, to page 16, line 3; page 17, line 11, to page 18, line 35; page 23, lines 1-8; and Figures 1 and 7.

Claims 2-4 have been amended to state that the cassettes are expressed in a transgenic animal or in a recombinant AAV vector. Support for these amendments is found throughout the application, for example, at page 11, lines 17-18; page 12, line 3, to page 13, line 21; page 16, line 21, to page 17, line 11; page 19, line 31, to page 23, line 18; and page 25, line 15, to page 33, line 7.

Support for the amendment to Claim 15 is found throughout the application, for example, at page 4, lines 2-4; page 17, lines 14-19; page 19, lines 11-12 and 28-30; and page 22, lines 3-5 and 25-32.

Support for the amendment to Claim 24 is found throughout the application, for example, at page 19, lines 18-20, and page 20, lines 4-16.

In view of the above, none of the foregoing additions or deletions from the claims are believed to constitute the addition of new matter to the application. In accord with the amendments and the following remarks, the examiner is respectfully requested to reconsider the patentability of the claims pending in this application.

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Rejections Under 35 U.S.C. §112, First Paragraph

Claim 11 has been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description rejection. As Claim 11 has been canceled from the application, this ground for rejection is now moot and applicants request that it be withdrawn.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 2-6 and 26 stand rejected under 35 U.S.C. §112, second paragraph. Claims 5, 6, and 26 have been canceled; hence the rejections under 35 U.S.C. S 112, second paragraph, are moot as regards these claims.

Claims 2-4 in particular were rejected in view of the examiner's position that essential elements are missing from the claims, namely, a structural element that would account for long-term expression of the cassette. This matter has been addressed by amendments specifying that the cassettes are expressed in a transgenic animal or a recombinant AAV vector. Accordingly, the examiner is respectfully requested to remove this ground for the rejection of Claims 2, 3, and 4.

Rejections Under 35 U.S.C. §102

*Miao et al.*

Claims 1-9, 12-16, 18, 20-24, and 26-31 are rejected under 35 U.S.C. § 102(a) as being anticipated by Miao et al. (*Mol. Ther.*, June 2000). Of this group of claims, all except Claims 1-4, 15, 16, and 24 have been canceled from the application. Accordingly, this ground for rejection is now moot as applied to Claims 5, 6, 7-9, 12-14, 18, 20-23, and 26-31.

The examiner states that she learned through a telephone call to the publisher that Miao et al. (2000) was published on June 13, 2000. However, in conjunction with a corresponding European case, the applicants some time ago obtained a letter from the publisher regarding the publication date of this same article. A copy of this letter is attached hereto as Exhibit A. According to this letter, the article in question was not mailed to subscribers until June 26, 2000,

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and was not available online until June 30, 2000. Barring written evidence to the contrary, this letter should be accepted as demonstrating that the effective publication date of Miao et al. (2000) was not earlier than June 26, 2000. The priority date of the present application is June 20, 2000; thus Miao et al. is not prior art with respect to this application. Accordingly, the examiner is respectfully requested to remove the rejection of Claims 1-4, 15, 16, and 24 under 35 U.S.C. § 102(b) over Miao et al. (2000).

*Fazio et al.*

Claims 1-4, 7-9, 17-20, and 27-30 are rejected as being anticipated by Fazio et al. (1993) as evidenced by Simonet et al. (1993) and Dang et al. (1995). Of this group of claims, all but Claims 1-4 have been canceled from the application. Hence, this ground for rejection is moot with respect to Claims 7-9, 17-20, and 27-30.

Prior to the amendments indicated above, Claim 24 claimed "the expression cassette of Claim 1, wherein the polyadenylation signal consists of the nucleic acid sequence set forth in SEQ ID NO: 6." Claim 24 was not included in the rejection over Fazio et al. (1994) as evidenced by Simonet et al. (1993) and Dang et al. (1995). The cassettes of amended Claim 1 now include the limitation that was deleted from Claim 24, that is, the polyadenylation signal of SEQ ID NO: 6. By not rejecting Claim 24 over Fazio et al., the examiner has indicated that this reference does not anticipate cassettes containing this polyadenylation signal. Accordingly, the examiner is respectfully requested to remove the rejection of amended Claim 1, and of Claims 2-4, which depend therefrom, under 35 U.S.C. § 102(b) over of Fazio et al. (1994) as evidenced by Simonet et al. (1993).

*Simonet et al.*

Claims 1-4, 7-9, 17-19, and 27-30 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Simonet et al. (1994) as evidenced by Simonet et al. (1993). Of these claims, all

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except Claims 1-4 have been canceled from the application. Hence, this ground for rejection is moot with respect to Claims 7-9, 17-19, and 27-30.

Prior to the amendments indicated above, Claim 24 claimed "the expression cassette of Claim 1, wherein the polyadenylation signal consists of the nucleic acid sequence set forth in SEQ ID NO: 6." Claim 24 was not included in the rejection over Simonet et al. (1994) as evidenced by Simonet et al. (1993). Amended Claim 1 now includes the limitation that was deleted from Claim 24, that is, the polyadenylation signal of SEQ ID NO: 6. By not rejecting Claim 24, the examiner has indicated that Simonet et al. (1994) does not anticipate cassettes containing this polyadenylation signal. Accordingly, she is respectfully requested to remove this ground for rejection of Claim 1, and of Claims 2-4, which depend therefrom, under 35 U.S.C. § 102(b) in view of Simonet et al. (1994) as evidenced by Simonet et al. (1993).

Rejections Under 35 U.S.C. §103

Claims 1-10 and 12-31 are rejected under 35 U.S.C. § 103(a) over Snyder et al. (U.S. Patent No. 6,936,243) as evidenced by two papers by Simonet et al. and by Nguyen et al., in view of Jallat et al. (1990) and Kurachi et al. (1995). Of these claims, all except Claims 1-4, 15, 16, and 24 have been canceled from the application; hence this ground for rejection is moot with respect to Claims 5-10, 12-14, 17-23, and 25-31.

According to the examiner, Snyder et al. discloses all of the elements of the claimed invention except for the use of a Factor IX intron in the nucleic acid expression cassette. Jallat et al. and Kurachi et al. are cited for teaching that Intron I or a fragment of this intron can increase the expression of Factor IX. However, applicants have shown that the expression cassette as claimed in amended Claim 1 was unexpectedly effective at expressing Factor IX protein in liver cells. For example, the specification at page 20, lines 18-24, discloses that:

> Most interestingly, when the ApoE-HCR element (SEQ ID NO: 4) and hAAT-promoter (SEQ ID NO: 5) were used in combination with the FIX minigene

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sequence (LX-ApoE-HCR-hAAT-FIXmg-bpA), Factor IX levels were ~67 fold higher (0.7-1.5 μg/ml) than the basal level obtained from animals receiving the LX-FIX construct. This level of Factor IX expression, ~30% of the normal plasma Factor IX concentration (5 μg/ml), was in a concentration that would be curative for individuals with hemophilia B.

The unexpected effectiveness of this expression cassette for expressing Factor IX protein rebuts the examiner's assertion that this construct is obvious in view of the cited references.

In view of the above remarks, the examiner is respectfully requested to withdraw the rejection of Claim 1 and claims depending therefrom (Claims 2-4, 15, 16, and 24) under 35 U.S.C. § 103(a) over Snyder et al. (U.S. Patent No. 6,936,243) in view of Jallat et al. and Kurachi et al.

Conclusion

In consideration of the above remarks and amendments, applicants believe that the claims in their present form are in condition for allowance and notification to that effect is respectfully requested.

Respectfully submitted,

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16 November 2004

**Washington Research Foundation**
c/o Beth G. Etscheid, Director of Licensing
2815 Eastlake Avenue East, Suite 300
Seattle, WA 98102-3096, USA

Dear Dr. Etscheid:

Per your forwarded request from the European Patent Office, find below applicable dates relating to product *Molecular Therapy* (YMTHE: 12877), most specifically its June 2000 product: Volume 1, Number 6.

Please note that *Molecular Therapy* in June 2000 was a product of Academic Press, which became part of Elsevier Inc. during the 2001 calendar. Hence, online posting date to Elsevier Inc. platform has also been included.

- Date printed issue entered mail to subscribers: **Monday, 26 June 2000**
- Date online product posted to Academic Press platform (IDEAL): **Friday, 30 June 2000**
- Date online product transferred to Elsevier Inc. online platform (ScienceDirect): **Tuesday, 22 July 2003**

If you require signed hard copy of same notice, please advise directly.

Best,

P. D. R.

Paul D. Richmond

*****

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**EXHIBIT A**